Derivation and Characterization of Cancer Stem Cells from Human ES Cells

Grant Award Details

Derivation and Characterization of Cancer Stem Cells from Human ES Cells

Grant Type: SEED Grant

Grant Number: RS1-00228

Project Objective: To generate cancerstem cells (CSC) from hESC to provide an experimental model system to study CSCbiology and ultimately find CSC specific therapies

Investigator:

Name:	Catriona Jamieson
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Blood Cancer, Cancer

Human Stem Cell Use: Cancer Stem Cell, Embryonic Stem Cell

Cell Line Generation: Cancer Stem Cell

Award Value: $616,305

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Derivation and Characterization of Cancer Stem Cells from Human ES Cells

Public Abstract:

Cancer is the leading cause of death for people younger than 85 (1). High cancer mortality rates underscore the need for more sensitive diagnostic techniques as well as therapies that selectively target cells responsible for cancer propagation (1) Compelling studies suggest that human cancer stem cells (CSC) arise from aberrantly self-renewing tissue specific stem or progenitor cells and are responsible for cancer propagation and therapeutic resistance (2-9). Although the majority of current cancer therapies eradicate rapidly dividing cells within the tumor, the rare CSC population may be quiescent and then reactivate resulting in disease progression and relapse (2-9). We recently demonstrated that CSC are involved in progression of chronic phase chronic myelogenous leukemia (CML), a disease that has been the subject of many landmark discoveries in cancer research(19-30), to a more aggressive and therapeutically recalcitrant myeloid blast crisis (BC) phase. These CSC share the same cell surface markers as granulocyte-macrophage progenitors (GMP) but have aberrantly gained the capacity to self-renew as a result of activation of the Wnt/ï¢-catenin stem cell self-renewal pathway (4). Because human embryonic stem cells (hESC) have robust self-renewal capacity and can provide a potentially limitless source of tissue specific stem and progenitor cells in vitro, they represent an ideal model system for generating and characterizing human CSC (10-18). Thus, hESC cell research harbors tremendous potential for developing life-saving therapy for patients with cancer by providing a platform to rapidly and rationally test new therapies that specifically target CSC (2-18). To provide a robust model system for screening novel anti-CSC therapies, we propose to generate and characterize CSC from hESC (10-18). We will investigate the role of genes that are essential for initiation of CML such as BCR-ABL and additional mutations such as b-catenin implicated in CSC propagation (19-30). The efficacy of specific Wnt/b-catenin antagonists at inhibiting BCR-ABL+ human ES cell self-renewal, survival and proliferation alone and in combination with potent BCR-ABL antagonists will be assessed in sensitive in vitro and in vivo assays with the ultimate aim of developing highly active anti-CSC therapy that may halt cancer progression and obviate therapeutic resistance (4,31).

Statement of Benefit to California:

The research outlined in this proposal represents a unique opportunity for collaborations between investigators from disparate disciplines to use human embryonic stem cells to challenge an existing paradigm namely that leukemic blasts are responsible for progression of chronic myelogenous leukemia (CML) rather than leukemic stem cells (LSC). Current clinical diagnostic tests are not sufficiently sensitive to predict timing of progression for all patients with CML nor are they adequate for determining the type of therapeutic intervention required. Moreover, the primary therapy for CML, Abl kinase inhibition, was shown to be cardiotoxic when given long-term at high doses. Furthermore, amplification of BCR-ABL is not the sole event that occurs during CML progression to blast crisis. Identification and inhibition of molecular mutations responsible for the generation of LSC in CML blood and/or marrow may prevent progression to blast crisis (BC) and would represent an innovative, effective form of CML therapy. Modeling of LSC responsible for CML progression in human embryonic stem cells could have a significant impact on our understanding of the pathophysiology of CML, provide novel diagnostic and therapeutic modalities and improve the quality and possibly quantity of life of patients with CML. By using BCR-ABL transduced human embryonic stem cells, we will rigorously evaluate the LSC hypothesis and as a consequence, the additional molecular events required for progression to blast crisis CML. The ultimate aims of this grant are to develop more sensitive methods to predict leukemic progression and to identify novel molecular therapeutic targets through the development of LSC models using human embryonic stem cells. We aim to provide a robust, reproducible system for testing novel anti-LSC compounds alone and in combination in order to expedite the development of novel therapeutic agents for anti-LSC clinical trials at {REDACTED}. Not only may the translational research performed in the context of this grant speed the delivery of innovative anti-LSC therapies for Californians with leukemia, it will help to train California's future R&D workforce in addition to developing leaders in translational medicine. This grant will provide the personnel working on the project with a clear view of the importance of their research to cancer therapy and a better perspective on future career opportunities in California.

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